Evaluating associations between the benefits and risks of drug therapy in type 2 diabetes: A joint modelling approach

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Abstract

Objective: Precision medicine drug therapy seeks to maximise efficacy and minimise harm for individual patients. This will be difficult if drug response and side-effects are positively associated, meaning patients likely to respond best are at increased risk of side-effects. We applied joint longitudinal-survival models to evaluate associations between drug response (longitudinal outcome) and risk of side-effects (survival outcome) for patients initiating type 2 diabetes therapy.

Study Design and Setting: Participants were randomised to metformin, sulfonylurea or thiazolidinedione therapy in the ADOPT drug-efficacy trial (n=4,351). Joint models were parameterised for: 1) current HbA1c response (change from baseline in HbA1c); 2) cumulative HbA1c response (total HbA1c change).

Results: With metformin, greater HbA1c response did not increase risk of gastrointestinal events (Hazard ratio (HR) per 1% absolute greater current response 0.82 (95% confidence interval 0.67,1.01); HR per 1% higher cumulative response 0.90 (0.81,1.00)). With sulfonylureas, greater current response was associated with increased risk of hypoglycaemia (HR 1.41 (1.04,1.91)). With thiazolidinediones, greater response was associated with increased risk of oedema (current HR 1.45 (1.05,2.01); cumulative 1.22 (1.07,1.38)) but not fracture.

Conclusion: Joint modelling provides a useful framework to evaluate the association between response to a drug and risk of developing side-effects. There may be great potential for widespread application of joint modelling to evaluate the risks and benefits of both new and established medications.

Plain Language Summary

Purpose of study

- An overlooked question in precision / stratified medicine and when evaluating new medications is: are the benefits and risks of a drug associated?

- Joint longitudinal-survival models can be applied when, as in type 2 diabetes, drug response is measured by a longitudinal biomarker (HbA1c) and risks of side-effects can be represented as a time-to-event outcome.

What did we do and find?

- We used joint longitudinal-survival models to show novel associations between the benefit of greater drug response and the risk of common side-effects for 3 glucose-lowering medications for patients with type 2 diabetes.

- Greater drug response was associated with increased risk of hypoglycaemia with sulfonylureas and oedema with thiazolidinediones. In contrast there was no evidence of an increased risk of gastro-intestinal side-effects with metformin.

What do the findings mean?

- Joint models provide a novel, flexible and robust approach to study the associations between the risks and benefits of drug therapy.
- Precision / stratified medicine studies seeking to identify patients or subgroups likely to respond well to a drug should also evaluate whether the same patients are at increased risk of side-effects.

Introduction

There is increasing interest in applying a precision medicine approach to select the most appropriate drug for a patient or subgroup of patients, in order to either improve response or to reduce side-effects.[1 2] An important but overlooked question, particularly if side-effects are a result of the primary pharmacological effect of the drug, is whether the patients most likely to benefit are also at greatest risk of side-effects. Type 2 diabetes is an ideal candidate for precision medicine as there are many drug options to lower blood glucose (as measured by HbA1c), but each drug has a different mechanism of action and specific side-effects. However, the association between HbA1c response and side-effects is unknown for all drug options. If patients likely to have a greater HbA1c response to a specific drug are also at increased risk of side-effects this may limit the clinical utility of any precision approach to type 2 diabetes therapy.

To date, no robust framework has been proposed to evaluate the association between drug response and risk of side-effects. In type 2 diabetes, HbA1c is measured repeatedly over time (a longitudinal process), whilst side-effect risk can be modelled as a time-to-event process. In this scenario, joint longitudinal-survival modelling is the preferred approach to evaluate the association between both processes.[3-6] Joint models attempt to capture the true, unobserved, longitudinal trajectory (in reality HbA1c is measured intermittently and is subject to measurement error from random noise and biological variation). This means joint models can reduce bias and improve efficiency compared with simpler approaches.[5 7] Joint models have been applied in many diseases including recently in type 1 diabetes (autoantibodies and time to disease onset),[8-11] but not to our knowledge in type 2

diabetes, or more broadly to evaluate the association between drug response and risk of side-effects.

In this study we applied joint modelling to evaluate the association between drug response and risk of established side-effects for 3 widely used type 2 diabetes drugs, and thus further evaluate the potential for precision drug therapy in type 2 diabetes.

Material and Methods

Overview

Our aim was to understand whether the degree of glycaemic response to three common glucose-lowering drugs altered the risk of developing a side-effect. To answer this question we examined the association between two outcomes: 1) HbA1c response (as measured by change from baseline in HbA1c) and 2) risk of developing a side-effect (gastro-intestinal (GI) events, hypoglycaemia, oedema and fracture).

Setting and design

We used individual participant level data from the ADOPT randomised trial,[12] accessed through Clinical Trial Data Transparency Portal under approval from GSK (Proposal-930).[13] ADOPT was a prospective head-to-head drug trial including treatment-naïve participants with type 2 diabetes who were randomised to Metformin (MFN), the sulfonylurea (SU) glyburide or the thiazolidinedione (TZD) rosiglitazone (n=4,351 participants). The aim of ADOPT was to evaluate the long-term efficacy of the TZD compared to SU and MFN and the primary outcome was time to therapy failure (confirmed fasting plasma glucose ≥180 mg/dl). Study visits were every 2 months in year 1, then every 3 months up to 5 years. Clinically determined adverse events were recorded at each study visit, including records of GI events, hypoglycaemia, oedema and fracture. Biomarkers including HbA1c were recorded at each visit. ADOPT participants in the intention to treat population with a valid baseline HbA1c were eligible for our study. Participants were censored if they reached the trial primary endpoint of glycaemic failure, trial-recorded study withdrawal, or at 5 years after starting therapy as in the ADOPT main analysis.

Study outcomes

Our time-to-event outcomes were the first occurrence of 4 established drug-specific side-effects, over a 5 year period. For MFN the outcome of interest was a GI event, for SU it was a hypoglycaemia event (patient self-reported) and for TZD we evaluated oedema events and bone fractures.[12] Each drug and side-effect was analysed separately. We excluded patients with a pre-trial history of oedema from the oedema analysis (6% of patients), but pre-trial hypoglycaemia, gastro-intestinal and fracture records were not available to do the same for other side-effects. Due to the high number of GI events we repeated the GI analysis restricted to only moderate/severe and severe events as sensitivity analysis. The longitudinal outcome of interest was HbA1c response as measured by change from baseline in HbA1c (HbA1c at each study visit (%) – baseline HbA1c (%)). Throughout HbA1c percentages refer to absolute values rather than percentage changes. To test the specificity of our findings we repeated the analysis for each side-effect for the other drugs.

Statistical analysis

We used a joint model with two parameterisations (Models 1-2) and two standard time-to-event models (Models 3-4), for comparison, to evaluate the association between HbA1c response and the risk of developing a side-effect. A fundamental difference between each model was in the method to estimate HbA1c response, as illustrated in Figure 1. Each side-effect was evaluated separately and the same modelling approach was applied for each side-effect. Participants were followed-up for up to five years from randomisation. As we were assessing the association between side-effects and response, all participants required at least one pre-side-

effect HbA1c measure (meaning 4% of participants with very early side-effects were excluded from oedema analysis, 3% fracture, 20% hypoglycaemia, 12% GI). All models were adjusted for baseline HbA1c.[14] Model setups were as follows:

Joint longitudinal-survival models

We used a maximum likelihood joint longitudinal-survival model to simultaneously assess the association between HbA1c response (longitudinal process) and the risk of developing a side-effect (survival process). The joint model consisted of a two parts: a longitudinal submodel and a survival submodel linked through shared subject-specific random effects.[6]

In the general survival submodel, the hazard for patient i ($h_i(t)$) can be represented as:

$$h_i(t) = h_0(t)\exp(w_i^T\gamma + \alpha m_i(t)),$$

where $h_0(t)$ is the baseline hazard, w_i are baseline covariates, γ are regression coefficients, $m_i(t)$ is the "true, unobserved" longitudinal biomarker (estimated from the longitudinal submodel) and α quantifies the association between the longitudinal biomarker and the time-to-event process.[6]

We derived $m_i(t)$ from the observed HbA1c response data using a linear mixed effects model with a non-linear term for time (as HbA1c response is typically non-linear):

$$y_i(t) = m_i(t) + \epsilon_i(t)$$

$$= \beta_0 + \beta_1 N(t_i)_1 + \beta_2 N(t_i)_2 + \beta_3 \text{Baseline HbA1c} + b_{i0} + b_{i1} N(t_i)_1 + b_{i2} N(t_i)_2 + \epsilon_i(t),$$

where y_i is the observed HbA1c change from baseline and m_i the "true", unobserved HbA1c change from baseline. $N(t_i)_1 \; and \; N(t_i)_2$ denote the basis for a non-linear natural cubic spline of time with 1 internal knot at the 50th percentile of follow-up time (included in both the fixed and random effect parts of the longitudinal HbA1c submodel), b_i is a vector of subject specific random effects, $b_i \sim N(0, \widetilde{D})$ where $\widetilde{D}$ is the unstructured covariance matrix of random effects, ϵ_i is the vector of residuals, and $\epsilon_i \sim N(0, \sigma^2)$ where σ^2 is the covariance matrix of the residuals.[6] For models of hypoglycaemia with metformin and oedema with sulfonylureas we used a linear term for the random effect of time to achieve model convergence.

Model 1: Joint model current value (JMcv). To assess the association between the current value of HbA1c response and risk of side-effects (the standard formulation of the joint model) we incorporated m_i from the longitudinal submodel as a time-dependent covariate in the survival submodel:

$$h_i(t) = h_0(t) \exp\{\gamma_0 \text{Baseline HbA1c} + \alpha m_i(t)\}$$

Model 2: Joint model cumulative HbA1c (JMcum). To evaluate whether the risk of side-effects was associated with total rather than current HbA1c response we specified a second formulation of the joint model to assess the association between cumulative HbA1c response (total HbA1c response estimated as area-under-the-curve) and risk of side-effects, by including $\int_0^t m_i(s)\, ds\}$, the integral of the longitudinal HbA1c response trajectory up to time *t*, in the time-to-event submodel:[6]

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$$h_i(t) = h_0(t) \exp\{\gamma_0 \text{Baseline HbA1c} + \alpha \int_0^t m_i(s)\, ds\}$$

For models 1 and 2 we used a B-spline with 5 internal knots to flexibly model the baseline hazard function. We examined the fit of submodels using residual plots. Models 1 and 2 were fitted using the JM package in R.[16]

Model 3: Last-observation-carried-forward analysis (LOCF). We included observed HbA1c response (HbA1c at time *t* – baseline HbA1c) as a time-dependent covariate in a Cox proportional hazards model. This approach does not correct for measurement error and assumes HbA1c response is constant between measurements. Hazard ratios represent the increased risk of a side-effect for a 1-unit (%) absolute increase in the most recent value of HbA1c change from baseline at time *t*.

Model 4: single estimate of HbA1c response at 6 months (6mR). We evaluated the association between HbA1c response at six months and subsequent risk of developing a side-effect. In this two-stage approach we first estimated a single estimate of HbA1c response as a change score at 6 months. In the second stage we used this estimate as the exposure in a Cox hazards survival model with delayed entry to 6 months. Participants who developed a side-effect prior to 6 months or had no HbA1c record at 6 months were excluded from this analysis (Supplementary Table 4).

Ethics approval

Data for the ADOPT trial were accessed through the Clinical Trial Data Transparency Portal, with study approval from GlaxoSmithKline (Proposal 930).

Results

The most common side-effects were GI side-effects with metformin (37%), followed by hypoglycaemia with sulfonylurea therapy (26%). Thiazolidinedione side-effects were less common (oedema 13%, fracture 7%, Table 1). Median follow-up was greater than 2.5 years in each cohort. For other participant characteristics see Supplementary table 1. Each side-effect occurred more frequently on these therapies than on the comparator drugs (Supplementary table 2).

Joint-model associations between HbA1c response and risk of side-effects

GI events. With metformin we found consistent evidence for an association between greater HbA1c response and reduced risk of a GI side-effect (Figure 2a). We observed a similar association for moderate/severe GI events (20% of patients) and no association for severe GI events (3% of patients) (Supplementary table 3). We found no evidence of an association with thiazolidinediones and sulfonylureas (Table 2**,** Supplementary table 3).

Hypoglycaemia. With sulfonylureas we found greater current HbA1c response was associated with an increased risk of hypoglycaemia (Model 1:JMcv, Figure 2b). We found no evidence for an association between the risk of hypoglycaemia and cumulative HbA1c response (Model 2:JMcum). With thiazolidinedione therapy, although the absolute risk of hypoglycaemia was much lower than with sulfonylurea therapy (8% versus 26%), greater current and cumulative HbA1c response were associated with an increased risk of hypoglycaemia. There was no evidence of an association between response and hypoglycaemia with metformin (Table 2).

Oedema: With thiazolidinediones, greater current (Model 1:JMcv) and cumulative (Model 2:JMcum) HbA1c response were associated with an increased risk of oedema (Figure 2c). We found no evidence of an association between HbA1c response and risk of oedema with metformin and sulfonylureas (Table 2).

Fracture: With thiazolidinediones we found no evidence for an association between HbA1c response and the risk of a fracture (Figure 2d). There was also no evidence of an association with metformin and sulfonylureas (Table 2, Supplementary table 6).

Associations using standard time-to-event approaches

Results using the last-observation-carried-forward approach (Model 3:LOCF) were generally consistent with those from the current value joint model (Model 1:JMcv) (Table 2, Figure 2). The exception was for thiazolidinediones and oedema, for which, in contrast to the joint model, we found no evidence of an association using the LOCF model. Using Model 4:6mR (where HbA1c response was estimated from a single 6 month value) we found no evidence of any association between HbA1c response and risk of side-effects except for gastrointestinal events with Metformin (hazard ratio per 1% absolute increase in 6 month HbA1c response 0.74 (95% CI 0.60, 0.91, Supplementary Table 4-5).

Discussion

Our study shows joint modelling can be a useful approach for evaluating associations between the benefits and risks of drug therapy. Using joint models for longitudinal and time-to-event data we were able to show important differences in the associations between drug response and risk of established side-effects for three widely-used type 2 diabetes drugs. We also found differences in the association between each of current and cumulative drug response and risk of side-effects, suggesting underlying differences in the nature of associations for the different drugs. Our results have implications for any precision medicine approach to type 2 diabetes therapy. More generally, they highlight the potential for widespread application of joint longitudinal-survival modelling to evaluate the benefits and risks of both new and established medications.

Advantages and disadvantages of joint models to evaluate the association between drug response and risk of side-effects

We found a key advantage of joint modes to be their flexibility. Different specifications of the joint model gave important additional insight into the underlying nature of associations between HbA1c response and side-effects. These insights fitted with what is known about the pharmacological action of the different drugs. Current, but not cumulative, HbA1c response was associated with an increased risk of hypoglycaemia with sulfonylureas. This is expected as hypoglycaemia is a side-effect related to short term fluctuations in blood glucose, rather than long term exposure. In contrast, for oedema with thiazolidinediones, which is less likely to

relate to short-term fluctuations in blood glucose, we observed associations for both current and cumulative HbA1c response.

We also found associations with joint models that were missed by simpler approaches. With oedema with thiazolidinedione therapy there was no association using the last-observation-carried-forward approach but a clear association using both specifications of the joint model. This is likely due to the reduced bias and increased efficiency of the joint model compared with the last-observation-carried-forward approach which does not correct for measurement error in the longitudinal HbA1c response.[5 7] In general, hazard ratios using the last-observation-carried-forward approach had the same direction of association but were attenuated compared with those obtained from the current value joint model, in keeping with previous comparisons.[4 17] We found a single measure of HbA1c at 6 months was insufficient to show evidence of an association between HbA1c response and side-effects, with the exception of GI side-effects with metformin where the association was consistent with the joint model.

There are some settings where joint models may be more limited. ADOPT was a large randomised, double-blinded trial and in this dataset we found joint models to be useful to evaluate the association between response and relatively common side-effects. Increasingly, similar trial datasets are available for researchers to address secondary research questions.[13 18] It may be more challenging to apply joint modelling in other datasets. In particular, the potential of recording bias should be considered if conducting similar studies in electronic health records, although greater sample size may offer the opportunity to study rarer side-effects. Testing the

specificity of results to drugs known to cause the side-effect by comparison with 'negative control' drugs may be a useful starting point. Joint models may also be harder to apply to study associations between drug response and acute or allergic side effects that occur immediately after starting therapy. This was apparent in our analysis, as although we included over 1000 participants for each drug, participants who developed an early side-effect prior to their on-therapy HbA1c were excluded, and this is a particular limitation of our analysis of hypoglycaemia with sulfonylureas. Another limitation of the joint modelling framework applied in this study is the assumption of a fixed association between longitudinal HbA1c and risk of each side effect. Whilst inspection of residual plots indicated this was an appropriate strategy, it is certainly plausible that associations could change with therapy duration, and incorporating duration of therapy as a time-varying effect within the joint modelling framework would be of considerable interest. Similarly, an extension of the joint modelling framework to robustly incorporate drug dose could yield further insight to complement the response:side-effect associations evaluated in this study. Evaluating the impact of dose is a particular challenge in trials of drug efficacy such as ADOPT, as participants could be both uptitrated based on reaching glycaemic thresholds and down-titrated if a randomised medication was poorly tolerated.

Implications for a precision medicine approach to type 2 diabetes therapy

Our findings for the different drugs have implications for any future precision medicine approach to type 2 diabetes therapy. Greater metformin drug response was not associated with an increased risk of gastro-intestinal side-effects and this suggests great potential to target therapy if patients likely to have greater drug

response can be robustly identified.[19] However, targeting sulfonylureas and thiazolidinediones to patients may be difficult as good responders are likely to be at increased risk of, respectively, hypoglycaemia and oedema. Our findings highlight the vital importance of considering both differential drug response and risk of side-effects in precision medicine studies, and this has been overlooked in previous work.[20 21]

Our findings do not however preclude a precision medicine approach for sulfonylureas and thiazolidinediones. Identification of characteristics associated with either, but not both, improved drug response and lower risk of side-effects may allow the targeting of these therapies. Furthermore, decisions on therapy should ultimately be informed by absolute rather than relative risks of benefit or harm.[1] For example, if patients likely to respond well to a thiazolidinedione can be identified then a thiazolidinedione may still be an appropriate option for patients whose absolute risk of developing a side-effect is sufficiently low.

Comparison with other studies

To our knowledge this is the evaluation of the association between HbA1c response and risk of side-effects for any of the three drugs, except for hypoglycaemia with sulfonylureas. Our results for sulfonylureas are consistent with previous observational studies that have examined the association between hypoglycaemia and achieved on-therapy HbA1c (rather than HbA1c response).[22 23] In the ACCORD trial, participants with greatest HbA1c response at 4 months had a reduced rather than increased risk of hypoglycaemia, although this can be explained by the fact that

in ACCORD the participants with least initial response were more likely to be on Insulin, the therapy with by far the strongest association with hypoglycaemia.[24]

In this study we found an unexpected association between greater response to TZD therapy and increased risk of hypoglycaemia, but no evidence of an association with metformin response, which would have indicated a positive association between increased drug response and increased risk of hypoglycaemia was a more general characteristic of glucose-lowering therapy. This is an interesting finding and one for which there is not a clear biological explanation, and it would be of interest to examine whether the TZD association can be replicated in other datasets. The association between oedema and HbA1c response with thiazolidinediones is not unexpected as the mechanisms underlying both glucose-lowering and fluid retention are both thought to relate to PPARy stimulation.[25] With metformin there is no clear biological reason for the association between greater HbA1c response and a lower risk of gastro-intestinal events. One possible explanation is decreased drug adherence in patients experiencing mild gastro-intestinal symptoms prior to the event being recorded.

Future work

There is great potential to apply joint modelling to evaluate the association between drug response and risk of side-effects for the other drug options in type 2 diabetes and to study drug therapy in other diseases. Our findings also suggest a potential application of joint modelling as an efficient tool for understanding the risk-benefit trade-off at the individual-level in drug development.[26] For precision medicine, the joint models used in this study could be extended to explore clinical features and

biomarkers associated with drug response, risk of side-effects, or both.[27 28] Alternative model specifications, such as evaluation of the effect of HbA1c response slope,[6] the weighting of cumulative HbA1c effects by recency,[15] the incorporation of multiple longitudinal biomarkers,[29] or incorporation of time-varying drug effects, may provide further insight into the nature of associations between response and side-effects. Similarly, incorporation of robust dose adjustment within the joint modelling framework, for example testing weighted cumulative drug associations,[30 31] could allow much greater understanding of the impact of different levels of drug exposure on both response and adverse events. These are areas of current methodological development; a general mathematical presentation of joint modelling for simultaneously evaluating risks and benefits of medication would be a useful next step.

Conclusions

Joint modelling is a useful and efficient method to evaluate associations between continuous drug response and time to side-effects. Our study suggests the potential for application of joint modelling in both drug development and precision medicine research to evaluate the benefits and risks of medications. In type 2 diabetes, any future precision approach to sulfonylurea and thiazolidinedione therapy should consider the likely increased risk of respectively, hypoglycaemia and oedema, if targeting these therapies at patients likely to have the greatest drug response.

Abbreviations

ADOPT – A Diabetes Outcome Progressing Trial

GSK – GlaxoSmithKline

HbA1c - Glycated haemoglobin

MFN – Metformin

SU - Sulfonylurea

TZD - Thiazolidinedione

Data statement

No additional data are available from the authors although the individual participant data from the ADOPT trial used in this study are available from GlaxoSmithKline on application via www.clinicalstudydatarequest.com

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Competing interests

WEH declares a grant from IQVIA, ERP declares personal fees from Lily, Novo Nordisk, and Astra Zeneca. For all other authors there are no other potential conflicts of interest relevant to this article.

Contributions

JMD, ATH, BMS and WEH designed the study. JMD analysed the data. JMD and WEH drafted the article. ATH, BMS, AGJ and ERP provided support for the analysis and interpretation of results, and critically revised the article. All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. WEH is the guarantor.

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Table 1: Participant Numbers and Study Follow-up for each Primary Drug:Side-effect Cohort (Models 1-3). Data are median (IQR) unless stated. See Supplementary table 4 for participants included in Model 4).

	Metformin - GI	SU - Hypo	TZD - Oedema	TZD - Fracture
No. of participants	1200	1052	1241	1311
No. of events (%)	440 (37%)	270 (26%)	164 (13%)	88 (7%)
Baseline HbA1c %	7.3 (6.7;7.9)	7.3 (6.7;7.9)	7.3 (6.7;7.9)	7.3 (6.7;7.9)
No. recorded HbA1c	13 (6;19)	12 (5;19)	18 (9;20)	18 (10;21)
Study follow-up (years)	2.8 (1.0;4.2)	2.5 (0.9;4.2)	4.0 (1.8;4.7)	4.0 (2.1;4.7)

Table 2: Hazard ratios for the Association between HbA1c Response and Risk of Side-effects (Models 1-3). Hazard ratios (95% Confidence Intervals) represent the increase in risk of a side-effect for a 1% greater absolute HbA1c response**.** A hazard ratio greater than 1 indicates an increased risk of a side-effect with greater HbA1c response.

Side-effect	**Model 1: JMcv**	**Model 2: JMcum**	**Model 3: LOCF**
		MFN	
Gastrointestinal	**0.82 (0.67, 1.01), *P*=0.06**	**0.90 (0.81, 1.00), *P*=0.06**	**0.85 (0.74, 0.96), *P*=0.01**
Hypoglycaemia	1.01 (0.63, 1.62), *P*=0.96	1.22 (0.93, 1.60), *P*=0.15	1.19 (0.88, 1.60), *P*=0.25
Oedema	1.16 (0.70, 1.92), *P*=0.58	1.09 (0.88, 1.36), *P*=0.42	1.07 (0.74, 1.56), *P*=0.71
Fracture	0.83 (0.48, 1.44), *P*=0.51	1.00 (0.78, 1.27), *P*=0.98	0.98 (0.69, 1.39), *P*=0.92
		SU	
Gastrointestinal	0.88 (0.69, 1.11), *P*=0.28	1.03 (0.92, 1.17), *P*=0.58	0.90 (0.77, 1.05), *P*=0.19
Hypoglycaemia	**1.41 (1.04, 1.91), *P*=0.03**	**1.09 (0.93, 1.29), *P*=0.28**	**1.41 (1.12, 1.77), *P*=0.003**
Oedema	1.31 (0.85, 2.02), *P*=0.23	1.09 (0.87, 1.36), *P*=0.45	0.87 (0.67, 1.13), *P*=0.28
Fracture	1.16 (0.70, 1.92), *P*=0.58	1.09 (0.88, 1.36), *P*=0.42	1.00 (0.64, 1.58), *P*=0.68
		TZD	
Gastrointestinal	1.21 (0.94, 1.55), *P*=0.13	1.05 (0.93, 1.18), *P*=0.44	1.04 (0.87, 1.26), *P*=0.65
Hypoglycaemia	1.98 (1.25, 3.15), *P*=0.004	1.37 (1.11, 1.7), *P*=0.003	1.44 (0.98, 2.12), *P*=0.07
Oedema	**1.45 (1.05, 2.01), *P*=0.03**	**1.22 (1.07, 1.38), *P*=0.003**	**1.01 (0.80, 1.27), *P*=0.94**
Fracture	**1.10 (0.72, 1.68), *P*=0.65**	**1.09 (0.93, 1.29), *P*=0.28**	**1.05 (0.72, 1.52), *P*=0.81**

Figure legends

Figure 1: Approaches to estimating HbA1c (%) response

Model 1: estimate current HbA1c response using a joint model (red line with black dotted 95% confidence intervals).
Model 2: estimate cumulative HbA1c response using a joint model (grey shaded area).
Model 3: carry forward the most recently observed value of HbA1c response until the next measurement (LOCF approach, black step function).
Model 4: take the observed HbA1c response at a single time point of 6 months (blue line).

Figure 2: Hazard ratios for the association between HbA1c response and risk of a drug-specific side-effect (Models 1-3). Hazard ratios (95% confidence intervals) represent the increase in risk of a side-effect for a 1% greater absolute HbA1c response**.** A hazard ratio greater than 1 indicates an increased risk of a side-effect with greater HbA1c response.